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WO 02/053188 A1

(54) **Title:** COMPOSITIONS COMPRISING CYCLODEXTRINS AND NO-RELEASING DRUGS

(57) **Abstract:** The present invention relates to composition comprising cyclodextrins and a NO-releasing drug of formula, A-X-L-NO_n, wherein A is the radical deriving from a drug; X is a divalent radical connecting A with the NO-releasing group L-NO_n; L is selected from the group consisting of: O and S; n is 1 or 2.

Compositions comprising cyclodextrins and NO-releasing drugs

Field of the Invention

The present invention relates to compositions comprising a NO-releasing derivative of a pharmaceutically active compound.

Background of the Invention

In the last decade there has been a growing interest towards the preparation and the properties of compounds comprising a radical derived from a compound having pharmaceutical activity and a NO releasing group.

EP 670 82, EP 759 899 and EP 722 434 disclose nitric esters of non-steroidal antiinflammatory drugs (NSAIDs). These compounds present an improved activity and reduced side effects when compared to the drug without NO-releasing group.

WO 98/15568 discloses nitrate esters of corticoids. Also in this case a reduced toxicity is observed when the nitrate group is present.

Compounds comprising a radical derived from an antithrombotic drug and a NO-releasing group are described in WO 98/21193. The comparative data show that the introduction of the NO-releasing group causes an increase of activity of the drug.

WO 00/61537 discloses the preparation of drugs comprising a NO releasing group linked to, inter alia, anti-inflammatory, analgesic, bronchodilators, ACE-inhibitors, β-blockers, antineoplastic compounds. The use of a linking group presenting specific antioxidant properties allows the use of these drugs to patients affected by oxidative stress and/or endothelial dysfunction.

Thus, it is possible to say that the introduction of NO releasing groups has proven to be advantageous in many classes of drugs. However, the introduction of a NO releasing group often leads to a relevant drawback, i.e. a significant reduction in water solubility, that might lead to a slower adsorption rate of the drug in the human body. It is therefore desirable to find methods to improve the bioavailability of compounds comprising a radical derived from a compound having pharmaceutical activity and a NO-releasing group.

The use of cyclodextrin complexes in combination with NO releasing compounds is known from WO 95/29172. In that case, however, there was no radical derived from a compound having pharmaceutical activity in the molecule complexed with Cyclodextrin and, furthermore, the problem was to render the molecule stable to degradation. Thus, both the

type of compound and the technical problem solved by the patent application are quite different from the present case.

Summary of the invention

The present invention relates to compositions for pharmaceutical use comprising a cyclodextrin and a compound comprising a radical derived from a compound having pharmaceutical activity and a NO releasing group.

Detailed description of the invention

The invention relates to compositions comprising cyclodextrins and a NO-releasing drug of formula

$$A\text{-}X\text{-}L\text{-}NO_n$$

wherein **A** is the radical deriving from a drug;

X is a divalent radical connecting A with the NO-releasing group;

L is selected from the group consisting of: O and S; preferably it is O;

n is 1 or 2, preferably it is 2.

The syntheses of these compounds is described in the following patents, which are herewith incorporated by reference: US 5,861,426, WO 98/15568, US 5,621,000, WO 00/61537, WO 00/61541, WO 00/61604, US 5,703,073, US 6,043,233, US 6,057,347.

Cyclodextrins are cyclic oligosaccharides constituted by the union of from 6 to 12 glucose units through α(1,4) bonds. The word CD, used to indicate them, is usually preceded by a Greek letter that indicates the amount of glucose units (α corresponds to 6, β corresponds to 7, and so on).

A characteristic parameter of CDs is the diameter of the cavity wherein the compound is complexed.

For many purposes α-CD have a too small cavity (5 Å) to complex molecules of a medium size. This is why for many applications β-CD is preferred (diameter: 6 Å). The drawback of β-CD is its low solubility in water (18.5 g/l). To overcome the problem, probably caused by inter- and intramolecular hydrogen bonds between the hydroxyl groups, β CD derivatives have been prepared which present a considerably higher water solubility. In fact, it is known that the hydroxyl groups in the glucose units of CDs can be selectively reacted to prepare ethers, esters, ionic ethers (see for example the review "Physicochemical Characteristics and Pharmaceutical uses of Cyclodextrin Derivatives" D. Duchene et al., Pharmacueutical Technology International, June 1990).

The cyclodextrins to be used in combination with the compounds of formula A-X-L-NO_n are not particularly limited. Preferred examples of cyclodextrins useful in the present invention are: α-CD, dimethyl α-CD, trimethyl α-CD, β-CD, dimethyl β-CD, trimethyl β-CD, 2-hydroxypropyl β-CD, 3-hydroxypropyl β-CD, 2,3-dihydroxypropyl β-CD, γ-CD, dimethyl γ-CD, trimethyl γ-CD and polymeric CD.

In each particular case, it is possible to determine, with a few trials, which one is the most suitable cyclodextrin to be used in combination with a specific drug.

The molar ratio between the drug and the cyclodextrin can vary in a broad range. Preferably it is comprised between 1:10 and 10:1, more preferably between 3:1 and 1:3.

The composition according to the invention can be prepared in different ways. For example, it is possible to mix together the cyclodextrin and the NO-releasing drug in water. Due to the low solubility of most drugs, the drug is partly or fully dissolved when complexed with the CD. The solution is then dried and the solid recovered. It is also possible to use a cosolvent (e.g. ethanol) which is miscible with water and that solubilizes the drug. In another embodiment it is also possible to isolate the pure complex by using a two phase system: a lipophilic solvent wherein the drug is soluble, and water. The CD dissolves in the water phase, the drug in the lipophilic pahse. The complex CD-drug is formed at the interphase. If it is soluble in water, it is recovered from the water phase.

Finally, it is also possible to simply mix the drug and the CD in the solid state by using mixing and/or milling means well known in the art.

In a preferred embodiment, the drug used in the compositions according to the present invention, is selected from the following classes of compounds:

non steroidal antiinflammatory and analgesic drugs, antibacterial (antibiotics), antiviral, steroids, antineoplastic, β-adrenergics (agonists and blockers), antihyperlipoproteinemic, bone resorption inhibitors.

Non limiting examples of non-steroidal anti-inflammatory and analgesic drugs are:

Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, Paracetamol, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Ketorolac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen, Bermoprofen, CS-670, Zaltoprofen, Tenoxicam, Piroxicam, Meloxicam, Tenidap, Aceclofenac, Acemetacin, 5-amino-acetylsalicylic acid, Alclofenac, Alminoprofen, Amfenac, Bendazac, α-bisabolol,

Bromosaligenin, Bucloxic acid, Butibufen, Cinmetacin, Clidanac, Clopirac, Diflunisal, Ditazol, Enfenamic acid, Etofenamate, Felbinac, Fenclozic acid, Fendosal, Fentiazac, Fepradinol, Flufenamic acid, Flunixin, Flunoxaprofen, Flurbiprofen, Glucametacin, Glycol salicilate, Ibuproxam, Isofezolac, Isoxepac, Isoxicam, Lornoxicam, Meclofenamic acid, Mefenamic acid, Metiazinic acid, Niflunic acid, Oxaceprol, Oxaprozin, Oxyphenbutazone, Parsalmide, Perisoxal, Olsalazine, Pirprofen, Protizinic acid, Salacetamide, Salicilamide O-acetic acid, Salsalate, Suxibuzone, Tiaramide, Tinoridine, Tolfenamic acid, Tropesin, Xenbucin, Ximoprofen, Zomepirac, Tomoxiprol.

Non limiting examples of antibacterials (antibiotics) are:

Metronidazolo, Ethambutol, Cycloserina, Cloxyquin, Negamycin, Nitroxoline, Mupirocin, Myxin, Novobiocin, Spectinomycin, Sulbactam, Tigemonam, Tubercidin, Nifurpirinol, Nifurprazine, Glyconiazide, Isoniazide, Opiniazide, Clofazamine, Meclocycline, Minocycline, Sancicline, Tetracicline, Oxytretracycline, Chlortetracycline, Demeclocycline, Methacycline, Doxicycline, Clomocycline, Cinoxacin, Rolitetraciclyne, Pipaciclyne, Guamecycline, Lymecyclinem, Apiciclyne, Nalidixic acid, Cyprofloxacin, Enoxacin, Floroxacin, Pipemidic acid, Difloxacin, Perfloxacin, Enrofloxacin Nadifloxacin, Grepafloxacin, Lomefloxacin, Sparfloxacin, Clinafloxacin, Tosufloxacin, Trovafloxacin, Ofloxacin, Flumequine, Pazufloxacin, Rufloxacin, Norfloxacin, Cefroxadine, Cephradine, Cefaclor, Cefadroxil, Cefprozil Cefatrizine, Cefpiramide, Cephalexin, Cephaloglycin, Loracarbef, Pivcephalexin, Cephamandole, Moxalactam, Cefclidin, Cefepime, Cefuzopran, Ceftibuten, Cefpodoxime Proxetil, Cefotaxime, Cefcapene Pivoxil, Cefodizime, Ceftiofur, Ceftriaxone, Cefditoren, Cefmenoxime, Cefteram, Cefuzonam, Cefdinir, Cefetamet, Cefixime, Cefpirome, Ceftazidine, Cefminox, Cephalosporin, Cefotiam, Ceforanide, Cefazolin, Ceftizoxime, Cefazedone, Cefonicid, Ceftezole, Cephacetrile, Cephapirin, Fenbenicillin, Hetacillin, Quinacillin, Pivampicillin, Aspoxicillin, Mezlocillin, Amoxicillin, Ampicillin, Epicillin, Phenethamate Cyclacillin, Amdinocillin, Penicillin N, Apalcillin, Bacampicillin, Sultamicillin, Talampicillin, Lenampicillin, Benzyl penicillic acid, Carbenecillin, Carindacillin, Clometocillin, Cloxacillin, Dicloxacillin, Floxacillin, Metampicillin, Methicillin, Oxacillin, Penicillin O, Penicillin V, Pheneticillin, Piperacillin, Propicillin, Sulbenicillin, Ticarcillin, Meropenem, Panipenem, Imipenem, Aztreonam, Carumonan, Sulfabenzamide, Sulfacetamide, Sulfachloropyridazine, Sulfacytine, Sulfadiazine, 4'-(Methylsulfamoyl)sulfanilanilide, Sulfadicramide, Sulfadoxine, Sulfamethoxine,

Sulfaethidolo, Sulfaguanole, Sulfalene, Sulfamerazine, Sulfameter, Sulfamethazine, Sulfamethizolo, Sulfamethonide, Sulfamethoxazole, Sulfamethoxypyridazine, Sulfamethylthiazole, Sulfametrole, Sulfamoxolo, Sulfanilamide, N^4-Sulfanilylsulfanilamide, Sulfanilyurea, N-Sulfanil-3,4-xylamide, Sulfaperine, Sulfaphenazole, Sulfaproxyline, Sulfapyrazine, Sulfapyridine, 4-Sulfanilamido salicylic acid, Sulfasomizole, Sulfasymazine, Sulfathiazole, Sulfathiourea, Sulfisomidine, Sulfisoxazole, Acetyl sulfamethoxypyrazine, Sulfaguanidine, Mafenide, Succisulfone, p-Sulfanylbenzylamine, Dapsone, Acediasulfone, Thiazolsulfone, 2-p-Sulfanilylanilino-ethanol, Benzylsulfamide, p-Aminosalicylic acid, p-Aminosalicylic acid hydrazide, Phenyl aminosalicylate, 4-4'-sulfinyldianiline, Clindamycin, Lincomycin, Josamycin, Midecamycins, Rokitamycin, Spiramycins, Mikamycin B, Rosaramycin, Azithromycin, Clarithromycin, Erytromycin, Dirithromycin, Amikacin, Arbekacin, Dibekacin, Tobramycin, Dihydrostreptomycin, Streptomycin, Deoxydihydrostreptomycin, Trospectomycin, Spectinomycin, Micronomicin, Netilmicin, Apramycin, Sisomicin, Neomycin, Paromomycin, Ribostamycin, Rifampin, Rifapentine. Sulfachrysoidine, Sulfamidochrysoidine, Salazosulfadimidine.

Non limiting examples of antiviral drugs are:

Acyclovir, Amantadine, Cidofovir, Cytarabine, Didanosine, Dideoxyadenosine, Edoxuridine, Famciclovir, Floxuridine, Ganciclovir, Idoxuridine, Indanavir, Lamivudine, Kethoxal, MADU, Penciclovir, Ribavirin, Sorivudine, Stavudine, Trifluridine, Valacyclovir, Vidarabine, Xenazoic acid, Zaltacitabine, Zidovudine.

Non limiting examples of steroids are:

Budesonide, Hydrocortisone, Aclomethasone, Algestone, Beclomethasone, Betamethasone, Chlorprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone, Diflucortolone, Difluprednate, Fluazacort, Flucoronide, Flumethasone, Flunisolide, Fluocinolone acetonide, Flucinonide, Fluocortin butyl, Fluocortolone, Fluorometholone, Fluperolone acetate, Fluprednilene acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol propionate, Halomatasone, Halopredone acetate, Hydrocortamate, Loteprednol etabonate, Medrysone, Meprednisone, Methylprednisolone, Mometasone furoate, Paramethasone, Prednicarbate, Prednisone, Prednisolone 21-diethylaminoacetate, Prednisolone sodium phosphate, Prednival, Prednylidene, Rimexolone, Triamcinolone,

Triamcinolone acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone propionate, Mazipredone, Tixocortol, Triamcinolone hexacetonide, Ursodeoxycholic acid, Chenodeoxycholic, Mytatrienediol, Ethynil Estradiol, Estradiol, Mestranol.

Non limiting examples of antitumoral drugs are:
Antacitabine, Anthramycin, Azacitidine, 6-Azauridine, Carubicin, Chlorambucil, Chlorozotocin, Cytarabine, Daunomicin, Defosfamide, Denopterin, Doxifluridine, Doxorubicin, Droloxifene, Edatrexate, Eflornithine, Enocitabine, Epirubicin, Epitiostanol, Etanidazole, Etoposide, Fenretinide, Fludarabine, Fluorouracil, Gemcitabine, Hexestrol, Idarubicin, Lonidamine, Melphalan, 6-mercaptopurine, Methotrexate, Mitoxantrone, Mycophenolic acid, Pentostatin, Pirarubicin, Piritexim, Podophyllic acid, Puromycin, Retinoic acid, Roquinimex, Streptonigrin, Teniposide, Tenuazonic acid, Thiamiprine, Thioguanine, Tomudex, Topotecan, Trimetrexate, Tubercidin, Ubenimex, Zorubicin.

Non limiting examples of β-adrenergic compounds are:
Albuterol, Bambuterol, Bitoterol, Carbuterol, Clenbuterol, Chlorprenalina, Dioxethedrine, Ephedrine, Epinephrine, Etafredine, Ethylnorepinephrine, Fenoterol, Isoetharine, Isoprotenerol, Mabuterol, Metaproterenol, Pirbuterol, Salmeterol, Soterenol, Terbutalina, Tuloterol, Procaterol, Bufetalol, Acebutolol, Alprenolol, Arotinolol, Atenolol, Betaxolol, Bevantolo, Bucumolol, bufuralol, Bunitrolol, Bupranolol, Carazolol, Carteolol, Celiprolol, Epanolol, Indenolol, Mepindolol, Metoprolol, Nadolol, Nifenalol, Penbutolol, Pindolol, Pronethalol, Propanolol, Sotalol, Timolol, Toliprolol, Butofilol, Cervedilol, Cetamolol, Dilevalol, Esmolol, Labetalol, Metipranolol, Moprolol, Nebivolol, Oxprenolol, Practolol, Sulfinalol, Tertatolol, Tilisolol, Xibenolol, Eprozinol, Etophylline, Exoprenaline, Propoxyphilline, Reproterol, Rimiterol, 1-Teobrominacetic acid, Tetroquinol, Nadoxolol.

Non limiting examples of antihyperlipoproteinemic compounds are:
Atovarstatin, Cilastatin, Dermostatin A, Dermostatin B, Fluvastatin, Lovastatin, Mevastatin, Nystatin A_1, Pentostatin, Pepstatin, Sinvastatin

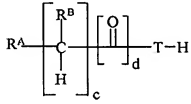
Non limiting examples of bone resorption inhibitors are:

Alendronic acid, Butedronic acid, Etidronic acid, Oxidronic acid, Pamidronic acid, Risedronic acid.

The chemical formula of the above listed compounds is reported on the Merck Index, Twelfth Edition.

Preferred drugs useful in the present invention are selected form the following formulas:

i)

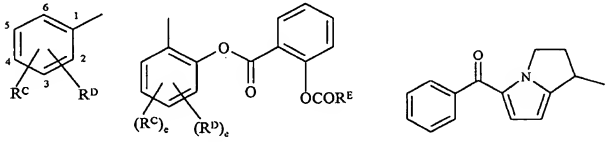


where **c** and **d** are independently 0 or 1;

T is selected from the group consisting of: O, NH and S;

$\mathbf{R^B}$ is selected from the group consisting of H, a linear or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl; preferably R^B is H, an alkyl having from 1 to 4 carbon atoms, most preferably R^B is CH_3

When **c** is equal to 0 , **d** is 1, $\mathbf{R^A}$ is selected from the group consisting of:



wherein:

$\mathbf{R^C}$ is selected from the group consisting of amino, R^ECONH-, $OCOR^E$ group, and the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from the group consisting of O, N, and S;

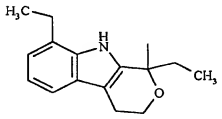
$\mathbf{R^E}$ is selected from the group consisting of methyl, ethyl and a linear or branched C_3-C_5 alkyl;

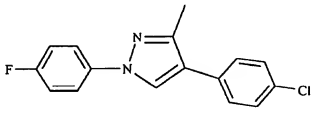
$\mathbf{R^D}$ is H, OH, halogen, a linear or when permissible branched alkyl having 1 to 4 atoms, a linear or when permissible branched alkoxyl having 1 to 4 atoms, a linear or when permissible

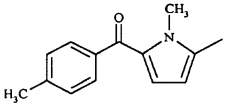
branched perfluoroalkyl having 1 to 4 carbon atoms, for example trifluoromethyl, amino, mono- or di-(C_1-C_4) alkylamino;

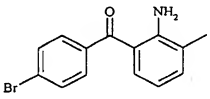
e is 0 or 1;

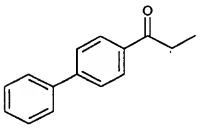
when **c** is equal to 1, **d** is equal to 1, $\mathbf{R^B}$ is hydrogen, $\mathbf{R^A}$ is selected from the group consisting of:

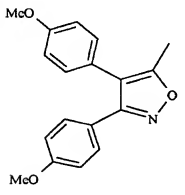


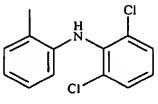


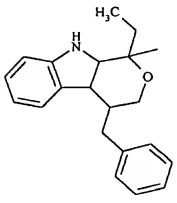


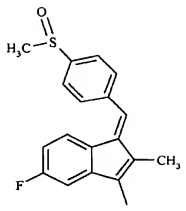


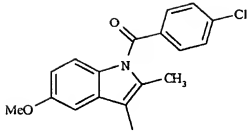




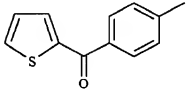


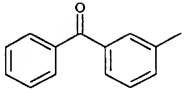


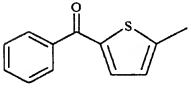


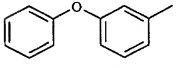


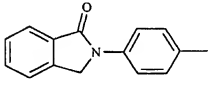
when **c** is equal to 1, **d** is equal to 1 and R^U is CH_3, R^A is selected from the group consisting of:

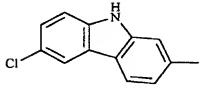


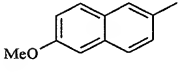


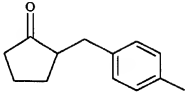


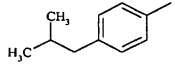


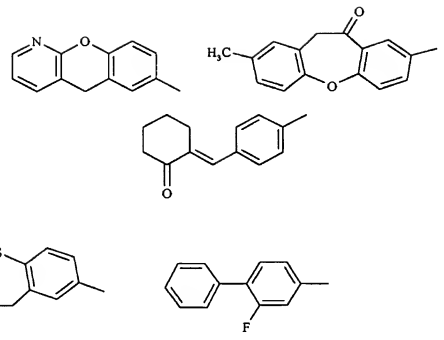




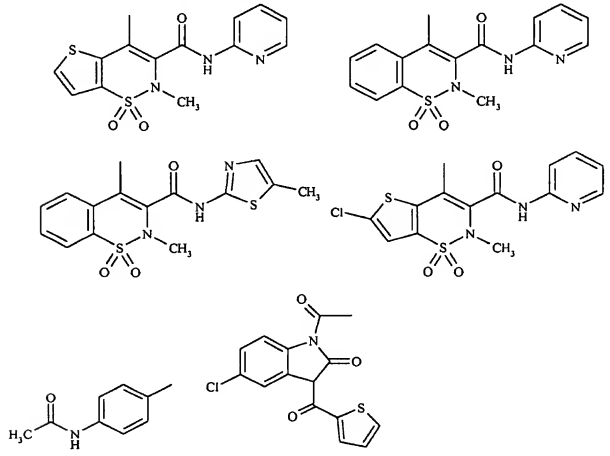




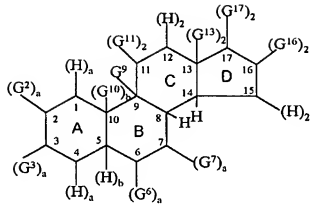




when **c** is equal to 0, **d** is equal to 0, R^A is selected from the group consisting of:



ii)



wherein:

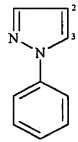
at the position 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 5-10 there may be a double bond; the ring A is optionally an aromatic ring;

a is equal to 1 or 2, **b** is equal to 0 or 1;

each G^2 is independently selected from the group consisting of H, Cl, Br;

each G^3 is independently selected from the group consisting of H, O-CH_3, O-CH_2-CH_2-Cl, OH; two G^3 can form a carbonyl group with the C^3 atom;

one G^2 and one G^3 can unite to form a ring of formula



wherein C^2=C^3 are part of the steroid structure;

each G^6 is independently selected from the group consisting of H, Cl, F, CH_3, -CHO;

each G^7 is independently selected from the group consisting of H, Cl, OH;

each G^9 is independently selected from the group consisting of H, Cl, F;

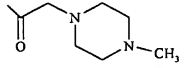
G^{10} is selected from the group consisting of H, Cl, F, CH_3, -CHO;

each G^{11} is independently selected from the group consisting of H, OH, , Cl; two G^{11} can form a carbonyl group with the C^{11} atom;

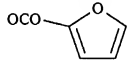
each G^{13} is independently selected from the group consisting of H, CH_3;

each G^{16} is independently selected from the group consisting of H, CH_3, OH; two G^{16} can form a vinyl group with the C^{16} atom;

each G^{17} is independently selected from the group consisting of H, OH and a monovalent radical comprising from 1 to 20 carbon atoms and from 0 to 5 oxygen, sulfur, nitrogen, halogen atoms; preferably it is H, OH, CH_3, C≡CH, CO-R-OH, CO-RH, CO-R-Cl, OCO-RH, CO-COO-RH, R-COOH, CH(OH)R-OH, COO-R-Cl, OC(O)O-RH, CO-R-SH, CO-R-O-CO-R-N$(CH_2CH_3)_2$, CO-SCH_2F, CO-R-OCORH,



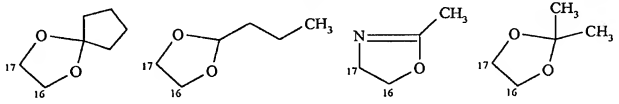
wherein R is a C_1-C_{20} linear or branched alkylene radical, and



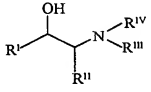
;

two G^{17} can form a carbonyl group with the C^{17} atom;

one G^{16} can unite with a G^{17} group to form, together with C^{16} and C^{17} the following groups:



iii)



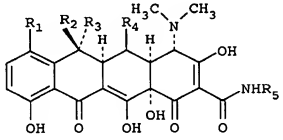
R^I is monovalent radical comprising from 6 to 20 carbon atoms and from 0 to 6 heteroatoms selected from oxygen, nitrogen, sulfur, chlorine, bromine, fluorine; examples of functional groups which are present in the radical R^I are the following: phenoxy, phenyl, thiazolyl, quinol-5-on-yl, pyridyl, tiofuranyl, tetrahydrofuranyl;

R^{II} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms, preferably R^{II} is selected from the group consisting of H, CH_3 and CH_3CH_2

R^{III} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms, preferably R^{III} is selected from the group consisting of H and CH_3;

R^{IV} is selected from the group consisting of hydrogen, a linear or branched alkyl having from 1 to 4 carbon atoms and a substituted aryl; preferably R^{IV} is selected from the group consisting of tert-butyl and isopropyl;

iv)



wherein:

R_1 is selected from the group consisting of H, Cl and dimethylamino,

R_2 is selected from the group consisting of H, OH,

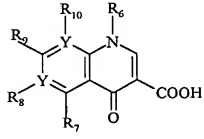
R_3 is selected from the group consisting of H, CH_3,

R_2 and R_3 together can be a methylene group (CH_2=),

R_4 is selected from the group consisting of H, OH,

R_5 is selected from the group consisting of H, CH_2OH and a monovalent radical containing from 5 to 20 carbon atoms and from 1 to 8 nitrogen atoms; the radical can further comprise other functional groups such as carboxyl and hydroxyl.

v)



wherein

each **Y** is independently selected from the group consisting of C and N,

R_6 is selected from the group consisting of cyclopropyl, phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-fluoroethyl and ethyl;

R_7 is selected from the group consisting of H, amino, methyl,

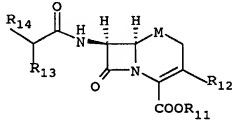
R_8 is selected from the group consisting of H and F;

R_9 is selected from the group consisting of H, methyl and a monovalent radical containing from 1 to 20 carbon atoms and from 1 to 4 nitrogen atoms;

R_{10} is selected from the group consisting of H, Cl and F;

R_6 e R_{10} can unite to form an optionally substituted six membered ring optionally containing up to two heteroatoms selected from the group consisting of oxygen and sulfur:

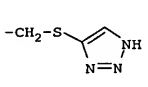
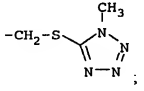
vi):



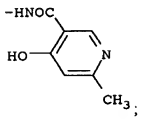
wherein

M is selected from the group consisting of sulfur, carbon or oxygen;

R_{11} is selected from the group consisting of H, pivaloyloxymethyl,

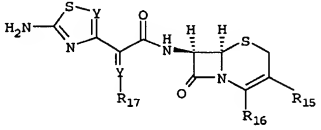
R_{12} is selected from the group consisting of chlorine and a monovalent radical containing from 1 to 5 carbon atoms, from 0 to 5 nitrogen atoms and from 0 to 1 sulfur atoms; preferably it is selected from chlorine, methyl, acetyloxymethyl, 2-propenyl  and  ;

R_{13} is selected from the group consisting of amino, hydroxyl and monovalent radical containing from 1 to 10 carbon atoms, from 0 to 5 oxygen atoms and from 0 to 5 nitrogen atoms;preferably it is selected from the group consisting of amino, hydroxyl, carboxyl and



R_{14} is an unsaturated C_6 ring, optionally substituted; preferably it is selected from the group consisting of phenyl, 1,4-cyclohexadienyl and 4-hydroxyphenyl.

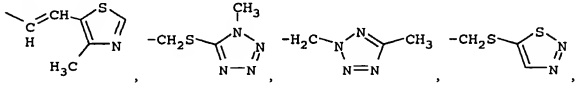
vii)

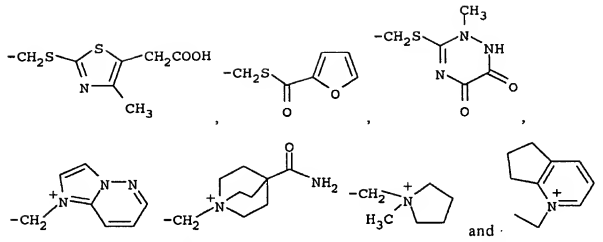


wherein:

each **Y** is independently selected from the group consisting of carbon and nitrogen

R_{15} is selected from the group consisting of hydrogen and a monovalent radical containing from 1 to 12 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of H, methyl, ethyl, ethenyl, NH_2COOCH_2-, CH_3COOCH_2-, pyridilmethylene and

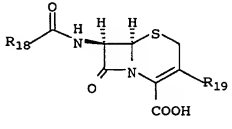




R_{16} is a monovalent radical containing from 1 to 10 carbon atoms and from 2 to 8 oxygen atoms; preferably it is selected from the group consisting of carboxyl, $(CH_3)_3CCOOCH_2OCO$- and $(CH_3)_2CHOCOOCH(CH_3)OCO$-; when R_{15} is a quaternary ammonium cation, R_{16} is optionally a $-COO^-$;

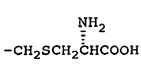
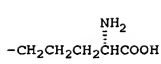
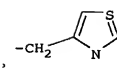
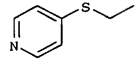
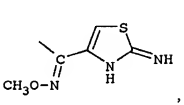
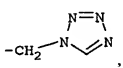
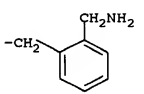
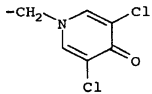
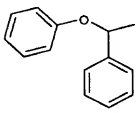
R_{17} is selected from the group consisting of -OH and a monovalent radical containing from 1 to 12 carbon atoms and from 0 to 4 oxygen atoms, preferably it is selected from the group consisting of -OH, $-OCH_3$, $-CH_2CH_3$, $-OCH_2COOH$, $-CH_2COOH$, $OC(CH_2)_3$-COOH.

viii)

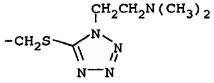
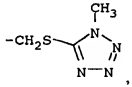
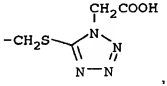
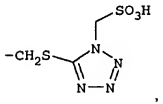
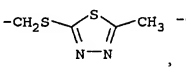
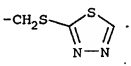


wherein:

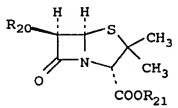
R_{18} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms; preferably it is selected from the group consisting of: PhCH(OH)-, $-CH_2CN$

R_{19} is selected from the group consisting of H and a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 6 nitrogen atoms and from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of: CH_3COOCH_2,

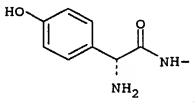
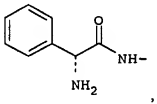
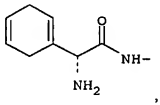
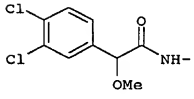
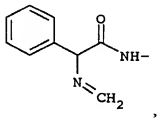
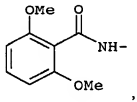
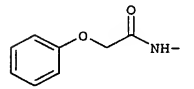
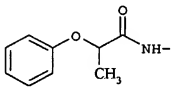
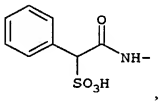
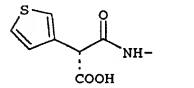
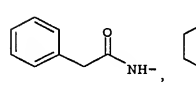







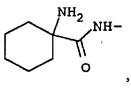
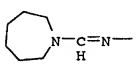
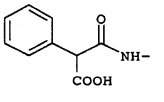
ix)

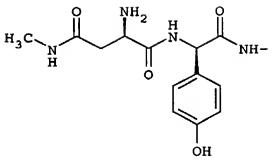


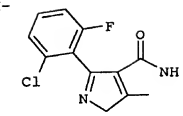
wherein:

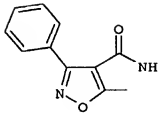
R_{20} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms, from 0 to 3 fluorine atoms and from 0 to 3 chlorine atoms; preferably it is selected from the group consisting of:

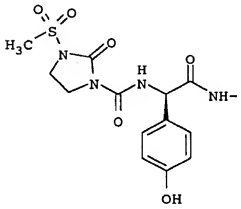












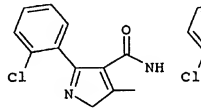




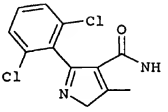


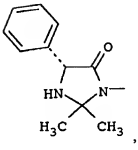


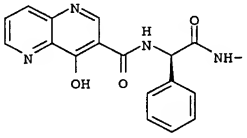


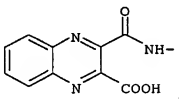


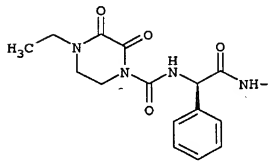










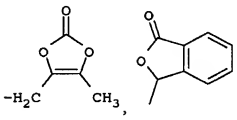


5

$$\text{-HNCO(CH}_2\text{)}_3\overset{\overset{\text{NH}_2}{|}}{\text{C}}\text{HCOOH}$$, -NHCO(CH$_2$)$_3$CH(NH$_2$)COOH, CH$_2$=CH$_2$SCH$_2$CONH-;

R_{21} is selected from the group consisting of H and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms and

from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of: H, -$CH_2OCOC(CH_3)_3$, -$CH(CH_3)OCOOC_2H_5$, -$CH_2CH_2N(CH_2CH_3)_2$,



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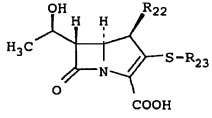
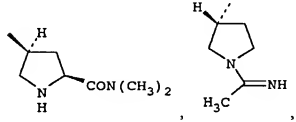
x)



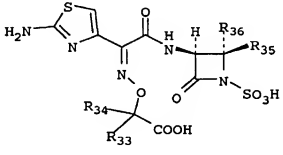
wherein:

R_{22} is selected from the group consisting of H and methyl;

R_{23} a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms and from 1 to 5 nitrogen atoms; preferably it is selected from the group consisting of: -$CH_2CH_2NHCH{=}NH$,



xi)

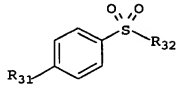


wherein:

R_{33} , R_{34} and R_{36} are independently selected from the group consisting of H and CH_3;

R_{35} is selected from the group consisting of H and $-CH_2OCONH_2$,

xii)



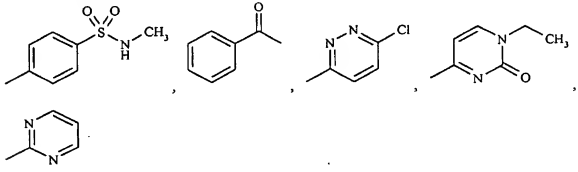
wherein:

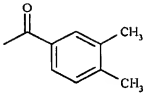
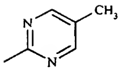
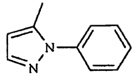
R_{31} is selected from the group consisting of $-NH_2$, $-CH_2NH_2$ and $-NHCH_2Ph$

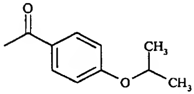
R_{32} is selected from the group consisting of $-NH_2$, $-NHR_{26}$ and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 5 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; wherein R_{26} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

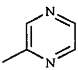
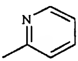
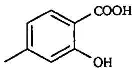
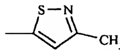
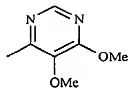
preferably R_{32} is selected from the group consisting of: 4-(2-hydroxyethylamino)phenyl, guanyl, 4-(amino)phenyl, 4-(aminomethyl)phenyl, 4-(carboxymethylamino)phenyl, succinylaminophenyl, 2-amino-5-thiazolyl;

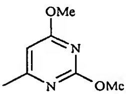
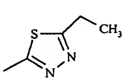
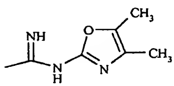
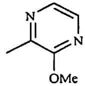
preferred examples of R_{26} are: acetyl, carbamoyl, 3-methyl-2-butenoyl, aminothioxomethylene,

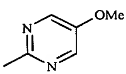
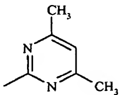
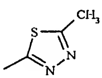
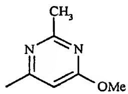


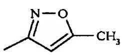
 ,  ,  ,

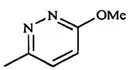
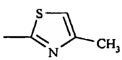
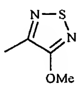
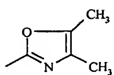
 ,

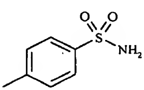
 ,  ,  ,  ,  ,

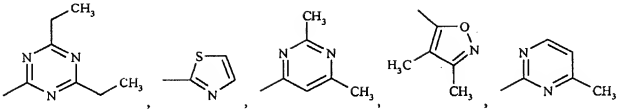
 ,  ,  ,  ,

 ,  ,  ,  ,

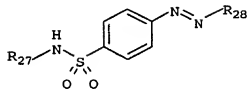
 ,

 ,  ,  ,  ,

 ,



xiii)

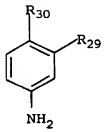


wherein:

R_{27} is selected from the group consisting of H and 4,6-dimethyl-2-pyrimidinyl;

R_{28} is a phenyl group substituted in at least 2 of the positions 2, 3, 4 and 6 by a group selected from hydroxyl, carboxyl and amino; preferred examples of R_{28} are 2,4-diamino-6-carboxyphenyl, 2,4-diaminophenyl, 3-carboxy-4-hydroxyphenyl;

xiv)

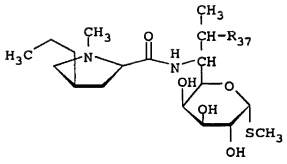


wherein:

R_{29} is selected from the group consisting of hydrogen and hydroxyl

R_{30} is selected from the group consisting of carboxyl, phenoxycarbonyl, 4-(amino)phenylsulfinyl, hydrazinocarbonyl;

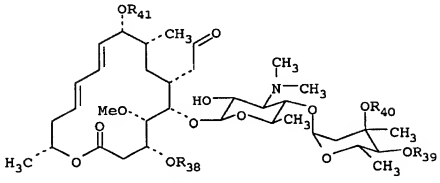
xv)



wherein:

R_{37} is selected from the group consisting of Cl and -OH;

xvi)

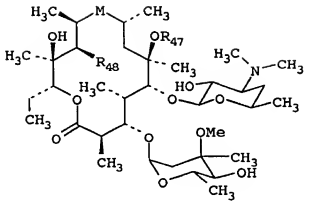


wherein:

R_{38} R_{39} R_{40} are independently selected from the group consisting of H and acyl; preferably they are selected from the group consisting of H acetyl, propionyl, butyrryl, valeryl

R_{41} is independently selected from the group consisting of H and

xvii)



wherein:

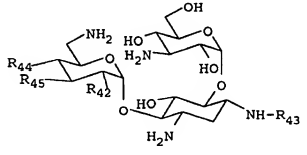
R_{47} is selected from the group consisting of H and $-CH_3$

M is selected from the group consisting of CO, N-methyl-aminomethylene and $-CH(NHR_{49})-$ wherein R_{49} is a substituted methylene bridge connecting N with R_{48}

R_{48} is hydroxyl or, when **M** is $-CH(NHR_{49})-$, is -O-;

Preferably R_{49} is  ;

xvii)



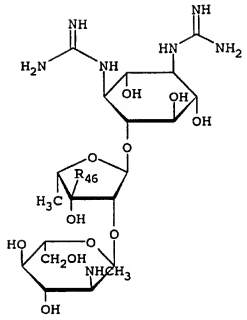
wherein:

R_{42} is selected from the group consisting of hydroxyl and amino;

R_{43} is selected from the group consisting of hydrogen, (R) and (S)-4-amino-2-hydroxybutyrryl

R_{44} and R_{45} are independently selected from the group consisting of hydrogen and hydroxyl.

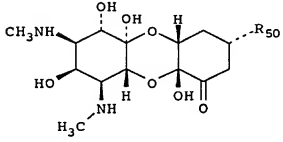
xviii)



wherein:

$\mathbf{R_{46}}$ is selected from the group consisting of $-CH_2OH$ and $-CHO$;

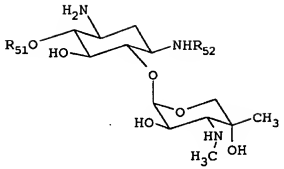
xix)



wherein:

$\mathbf{R_{50}}$ is a C_1-C_4 alkyl, preferably it is selected from the group consisting of methyl and n-butyl.

xx)

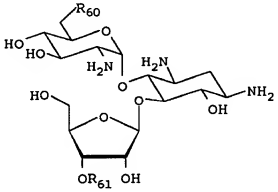


wherein:

R_{51} is independently selected from the group consisting of 3-amino-6-(aminomethyl)-3,4-dihydro-2H-pyran-2-yl and 2-amino-2,3,4,6-tetradeoxy-6-(methylamino)-α-D-eritro-hexopyranosyl,

R_{52} is selected from the group consisting of H and $-CH_2CH_3$.

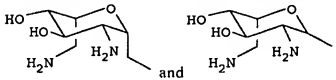
xxi)



wherein:

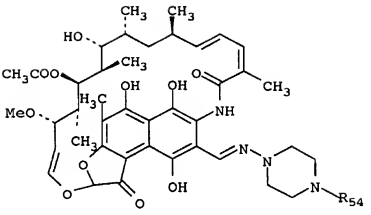
R_{60} is selected from the group consisting of –OH and $–NH_2$;

R_{61} is selected from the group consisting of H,



and

xxii)



wherein R_{54} is a C_1-C_4 linear or cyclic alkyl, preferably it is selected from the group consisting of methyl and cyclopropyl.

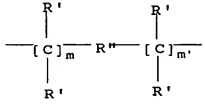
In a preferred embodiment **X** is a divalent radical having the following structure : (L')f-X', wherein

X' is a divalent radical comprising from 1 to 50 carbon atoms, from 0 to 10 nitrogen atoms, from 0 to 20 oxygen atoms, from 0 to 2 sulfur atoms and from 0 to 8 halogen atoms.

L' is selected from the group consisting of O, S, NR' and CO; with **R'** selected from the group consisting of H and linear and branched C_1-C_4 alkyl;

f is 0 or 1.

In a preferred embodiment X' is represented by the following formula:



wherein:

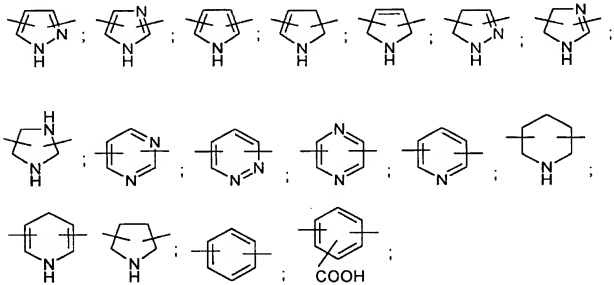
m is selected from 0, 1, 2 and 3; preferably it is 1;

m' is selected from 1, 2 and 3; preferably it is 1;

each **R'** is independently selected from the group consisting of H, linear and branched C_1-C_4 alkyl; preferably it is H;

R" is selected from the group consisting of: 5 and 6 membered saturated, unsaturated and aromatic heterocycles, phenyl, optionally substituted by a carboxylic group;

When R" is an heterocycle, it is preferably selected from the group consisting of the following divalent radicals:



More preferably R" is selected from the group consisting of a pyridyl and pyrazolyl radical , most preferably it is selected from the group consisting of 2,3-, 2,6- pyridyl and 3, 5-pyrazolyl radicals, wherein 2, 3, 5 and 6 indicate the positions connecting the ring to the carbons of the bridge.

In another preferred embodiment X' is a C_1-C_{20} alkylene group, preferably C_2-C_6, optionally substituted by - NH_2, -OH, $NHCOR^E$ wherein R^E is selected from the group consisting of methyl, ethyl, linear or branched C_3-C_5 alkyl; a C_5-C_7 cycloalkylene group, optionally substituted by one or more C_1-C_6 alkyl chains;

In a third preferred embodiment X' is selected from the group consisting of a group of formula :

-CHR'''-CHR'''-(O-CHR'''-CHR''')$_p$- and -CHR'''-CHR'''-CHR'''-(O-CHR'''-CHR''')$_p$-

wherein each **R'''** is independently selected from the group consisting of H and CH_3

p varies from 1 to 6, preferably from 1 to 4.

In another preferred embodiment the group X comprises a radical having specific antioxidant properties as disclosed in WO 00/61537, WO 00/61541, WO 00/61604.

Non limiting examples of compounds from which the antioxidant radical is derived are: Aspartic acid, Histidine, 5-Hydroxytryptophan, 4-Thiazolidincarboxylic acid, 2-Oxo-4-thiazolidincarboxylic acid, 2-Thiouracil, 2-Mercaptoethanol, Esperitine, Secalciferol, 1-α-OH-vitamin D2, Flocalcitriol, 22-Oxacalcitriol, 24,28-Methylene-1α-hydroxyvitamin D2, 2-Mercaptoimidazol, Succinic acid,

L-Carnosine, Anserine, Selenocysteine, Selenomethionine, Penicillamine, N-Acetylpenicillamine, Cysteine, N-acetyl-cysteine, Glutathione or its esters, Gallic acid, Ferulic acid, Gentisic acid, Citric acid, Caffeic acid, Hydrocaffeic acid, p-Coumaric acid, Vanillic acid, Chlorogenic acid, Kynurenic acid, Syringic acid, Nordihydroguaiaretic acid, Quercetin, Cathechin, Kaempferol, Sulphurethyne, Ascorbic acid, Isoascorbic acid, Hydroquinone, Gossypol, Reductic acid, Methoxyhydroquinone, Hydroxyhydroquinone, Propyl gallate, Saccharose, Vitamin E, Vitamin A, 8-Quinolol, 3-ter-Butyl-4-hydroxyanisole, 3-Hydroxyflavone, 3,5-ter-Butyl-p-hydroxytoluene, p-ter-Butyl-phenol, Timolol, Xibornol, 3,5-di-ter-Butyl-4-hydroxybenzyl-thioglycolate, 4'-Hydroxybutyranilide, Guaiacol, Tocol, Isoeugenol, Eugenol, Piperonyl alcohol, Allopurinol, Conyferyl alcohol, 4-Hydroxyphenetyl alcohol, p-Coumaric alcohol, Curcumin, N,N'-Diphenyl-p-phenylenediamine, Ethoxyquin, Thionine, Hydroxyurea, 3,3'-Thiodipronic acid, Fumaric acid, Dihydroxymaleic acid, Thioctic acid, 3,4-Methylendioxycinnamic acid, Piperonylic acid, N-Ethylendiethanolamine, Thiodiethylenglycol.

The following are non-limiting example which illustrate the invention.

Experimental

Example 1

Male Guinea pigs (weighing 300 to 500 g) were killed by a blown on the neck and exsanguinated. Urinary bladders were cut into strip preparations (3x12 mm). Guinea-pig bladder strips were rapidly transferred to jacketed tissue baths (25 ml) and mounted between two hooks. One the hooks was connected to a force transducer (Gould UC2). The strips were maintained at 37°C in a physiological salt solution. (PSS) that contains the following components: NaCl (119 mM), KCl (4.6 mM), $CaCl_2$ (1.5 mM), $MgCl_2$ (1.2 mM), $NaHCO_3$ (20 mM), NaH_2PO_4 (1.4 mM) and glucose (11 mM).The solution was gassed with a 95/5 mixture of O_2/CO_2 until a pH of 7.4 was achieved. A tension of 0.5 g was initially applied to each preparation. During stabilization (40-60') the strips were repeatedly washed and the tension was adjusted. Tissue contraction was induced by corbachol $3x10^{-6}$ M.

The experiment compares the inhibition of contraction obtained by using a solution of the composition according to the invention with the effect achieved by the same drug without cyclodextrin. Both the composition and the drug were dissolved in dimethylsulphoxyde (DMSO) and then added to the tissue bath were the their concentration was $1.0x10^{-5}$ M.

The drug used is 2-fluoro-α-methyl[1,1'-biphenyl]-4-acetic acid 4-(nitrooxy) butyl ester (NO-1).

F1and F2 represent the following compositions:

F1: 1.340 g of α CD and 0.500 g of NO-1 mixed in in water and then dried.

F2: 1.820 g of dimethyl β CD and 0.500 g of NO-1 mixed in water and then dried.

F0 represents the comparative test performed by using NO-1 alone (no CD).

The percentage of inhibition of contraction obtained were the following:

Composition	Inhibition (%)
F1	26.05
F2	31.52
F0 (comparative)	21.67

Example 2

Male Guinea pigs (weighing 300 to 500 g) were killed by a blown on the neck and exsanguinated. The thoracic aorta artery was isolated, placed in a ice cold PPS that contains the following components: NaCl (119 mM), KCl (4.6 mM), $CaCl_2$ (1.5 mM), $MgCl_2$ (1.2 mM), $NaHCO_3$ (20 mM), NaH_2PO_4 (1.4 mM) and glucose (11 mM), cleaned of connective tissue and cut into transverse ring (3mm). Each ring was then suspended vertically in the organ chamber (25 ml) and mounted between two hooks in PPS maintained at 37°C and gassed with a mixture 95/5 of O_2/CO_2 until achievement of a pH 7.4. One of the hooks was connected to a force transducer (Gould UC2). A resting tension of 2 g was initially applied to each preparation. During stabilization (45') the strips are repeatedly washed and the resting tension is adjusted.

Aorta rings were precontacted with phenylephrine $3x10^{-6}$ M and exposed to the drug at a concentration $1.0x10^{-6}$ M.

The experiment compares the inhibition of contraction effect achieved by using a solution of the composition according to the invention with the effect achieved by the same drug without cyclodextrin. Both the composition and the drug were dissolved in dimethylsulphoxyde (DMSO).

The drug used is 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester (NO-2).

F1, F2 and F3 represent the following compositions:

F1: 1.470 g of α CD and 0.500 g of NO-2 mixed in water and then dried.

F2: 1.470 g of α CD and 0.500 g of NO-2 mixed in ethanol/water and then dri ed.

F3: 2.000 g of dimethyl β CD and 0.500 g of NO-2 mixed in water and then dried.

F0 represents the comparative test performed by using NO-2 alone (no CD).
The percentages of inhibition obtained were the following:

Composition	Inhibition (%)
F1	54
F2	59
F3	61
F0 (comparative)	19

5

Claims

1. Composition comprising cyclodextrins and a NO-releasing drug of formula

$$A\text{-}X\text{-}L\text{-}NO_n$$

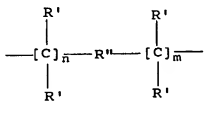
wherein **A** is the radical deriving from a drug;

X is a divalent radical connecting A with the NO-releasing group $L\text{-}NO_n$;

L is selected from the group consisting of: O, S and NH;

n is 1 or 2.

2. Composition according to claim 1 wherein $-L-NO_n$ is $-O-NO_2$
3. Composition according to claims 1-2 wherein the cyclodextrin is selected from the group consisting of α CD, dimethyl α CD, trimethyl-α CD, β CD, dimethyl-β CD, trimethyl-β CD, 2-hydroxypropyl-β CD, 3-hydroxypropyl-β CD, 2,3-dihydroxypropyl-β CD, γ CD, dimethyl γ CD, trimethyl γ CD and polymeric CD.
4. Composition according to claim 1-3 wherein the drug is selected from the following compounds: non steroidal antiinflammatory and analgesic drugs, antibacterial (antibiotics), antiviral, steroids, antineoplastic, β-adrenergics (agonists and blockers), antihyperlipoproteinemic, bone resorption inhibitors.
5. Composition according to claim 1-4 wherein **X** is a divalent radical having the following structure: $(L')_f\text{-}X'$, wherein **X'** is a divalent radical comprising from 1 to 20 carbon atoms, from 0 to 5 nitrogen atoms, from 0 to 5 oxygen atoms, from 0 to 2 sulfur atoms and from 0 to 5 halogen atoms and **L'** is selected from the group consisting of O, S, NR', CO, with **R'** selected from the group consisting of H, linear and branched C_1-C_4 alkyl; **f** is 0 or 1
6. Composition according to claim 5 wherein X' is represented by the following formula:



wherein:

n is selected from 0, 1, 2 and 3; preferably it is 1;

m is selected from 1, 2 and 3; preferably it is 1;

each **R'** is independently selected from the group consisting of H, linear and branched C_1-C_4 alkyl; preferably it is H;

R" is selected from the group consisting of: 5 and 6 membered saturated, unsaturated and aromatic heterocycles, phenyl, optionally substituted by a carboxylic group.

7. Composition according to claim 5 wherein X' is a C_1-C_{20} alkylene group, preferably C_2-C_6, optionally substituted by - NH_2, -OH, $NHCOR^E$ wherein R^E is selected from the group consisting of methyl, ethyl, linear or branched C_3-C_5 alkyl; a C_5-C_7 cycloalkylene group, optionally substituted by one or more C_1-C_6 alkyl chains;

8. Composition according to claim 5 wherein X' is selected from the group consisting of a group of formula :

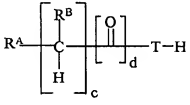
-CHR"'-CHR"'-(O-CHR"'-CHR"')$_p$- and -CHR"'-CHR"'-CHR"'-(O-CHR"'-CHR"'-CHR"')$_p$-

wherein each **R"'** is independently selected from the group consisting of H and CH_3

p varies from 1 to 6, preferably from 1 to 4.

9. Composition according to claims 1-8 wherein the drug is selected form the following formulas

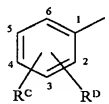
i)

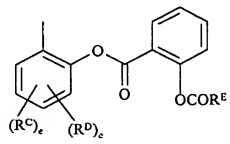


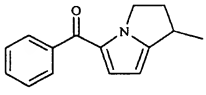
where **c** and **d** are independently 0 or 1;

T is selected from the group consisting of: O, NH and S;

$\mathbf{R^{II}}$ is selected from the group consisting of H, a linear or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl; When **c** is equal to 0 , **d** is 1, $\mathbf{R^A}$ is selected from the group consisting of:







25

wherein:

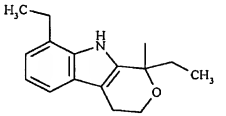
R^C is selected from the group consisting of amino, R^ECONH-, $OCOR^E$ group, and the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from the group consisting of O, N, and S;

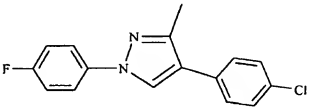
R^E is selected from the group consisting of methyl, ethyl and a linear or branched C_3-C_5 alkyl;

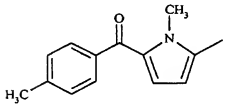
R^D is H, OH, halogen, a linear or when permissible branched alkyl having 1 to 4 atoms, a linear or when permissible branched alkoxyl having 1 to 4 atoms, a linear or when permissible branched perfluoroalkyl having 1 to 4 carbon atoms, for example trifluoromethyl, amino, mono- or di-(C_1-C_4) alkylamino;

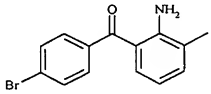
e is 0 or 1;

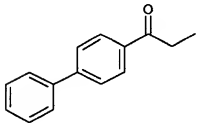
when **c** is equal to 1, **d** is equal to 1, R^B is hydrogen, R^A is selected from the group consisting of:

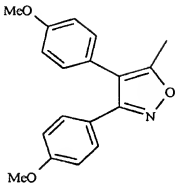


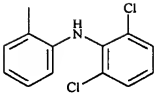


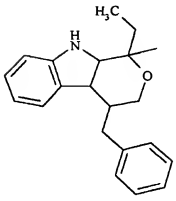


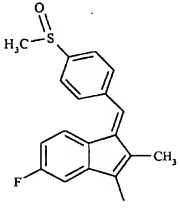


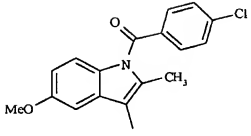




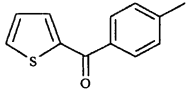


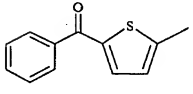


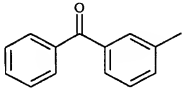


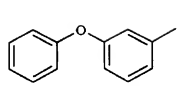


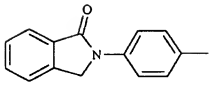
when **c** is equal to 1, **d** is equal to 1 and $\mathbf{R}^{B}$ is CH_3, $\mathbf{R}^{A}$ is selected from the group consisting of:

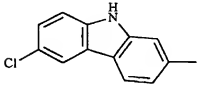


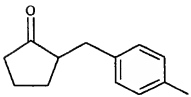


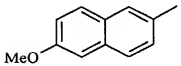


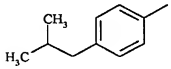


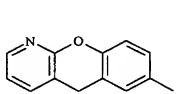


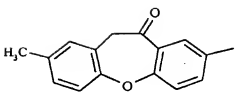


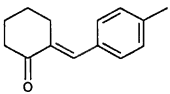


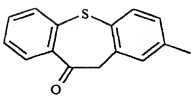


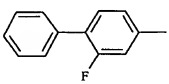




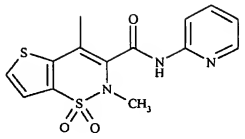


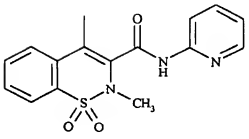


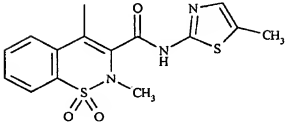


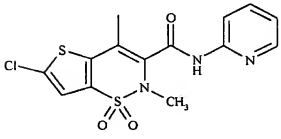


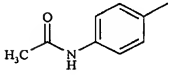
when **c** is equal to 0, **d** is equal to 0, $\mathbf{R^A}$ is selected from the group consisting of:

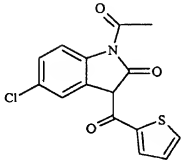




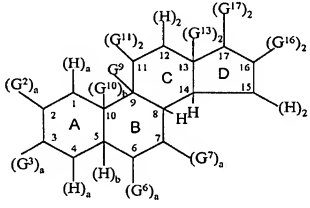








ii)



wherein:

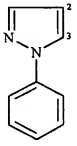
at the position 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 5-10 there may be a double bond; the ring A is optionally an aromatic ring;

a is equal to 1 or 2, b is equal to 0 or 1;

each G^2 is independently selected from the group consisting of H, Cl, Br;

each G^3 is independently selected from the group consisting of H, O-CH_3, O-CH_2-CH_2-Cl, OH; two G^3 can form a carbonyl group with the C^3 atom;

one G^2 and one G^3 can unite to form a ring of formula



wherein C^2=C^3 are part of the steroid structure;

each G^6 is independently selected from the group consisting of H, Cl, F, CH_3, -CHO;

each G^7 is independently selected from the group consisting of H, Cl, OH;

each G^9 is independently selected from the group consisting of H, Cl, F;

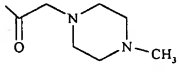
G^{10} is selected from the group consisting of H, Cl, F, CH_3, -CHO;

each G^{11} is independently selected from the group consisting of H, OH, , Cl; two G^{11} can form a carbonyl group with the C^{11} atom;

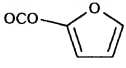
each G^{13} is independently selected from the group consisting of H, CH_3;

each G^{16} is independently selected from the group consisting of H, CH_3, OH; two G^{16} can form a vinyl group with the C^{16} atom;

each G^{17} is independently selected from the group consisting of H, OH and a monovalent radical comprising from 1 to 20 carbon atoms and from 0 to 5 oxygen, sulfur, nitrogen, halogen atoms; preferably it is H, OH, CH_3, C≡CH, CO-R-OH, CO-RH, CO-R-Cl, OCO-RH, CO-COO-RH, R-COOH, CH(OH)R-OH, COO-R-Cl, OC(O)O-RH, CO-R-SH, CO-R-O-CO-R-N(CH_2CH_3)$_2$, CO-SCH_2F, CO-R-OCORH,



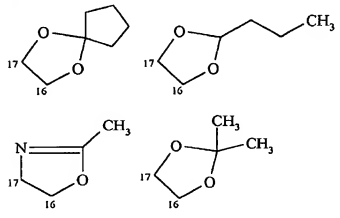
wherein R is a C_1-C_{20} linear or branched alkylene radical, and



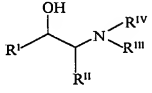
;

two G^{17} can form a carbonyl group with the C^{17} atom;

one G^{16} can unite with a G^{17} group to form, together with C^{16} and C^{17} the following groups:



iii)



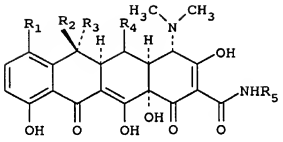
$\mathbf{R^I}$ is monovalent radical comprising from 6 to 20 carbon atoms and from 0 to 6 heteroatoms selected from oxygen, nitrogen, sulfur, chlorine, bromine, fluorine;

$\mathbf{R^{II}}$ is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms;

$\mathbf{R^{III}}$ is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms;

$\mathbf{R^{IV}}$ is selected from the group consisting of hydrogen, a linear or branched alkyl having from 1 to 4 carbon atoms and a substituted aryl; preferably R^{IV} is selected from the group consisting of tert-butyl and isopropyl;

iv)



wherein:

R_1 is selected from the group consisting of H, Cl and dimethylamino,

R_2 is selected from the group consisting of H, OH,

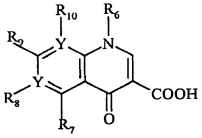
R_3 is selected from the group consisting of H, CH_3,

R_2 and R_3 together can be a methylene group (CH_2=),

R_4 is selected from the group consisting of H, OH,

R_5 is selected from the group consisting of H, CH_2OH and a monovalent radical containing from 5 to 20 carbon atoms and from 1 to 8 nitrogen atoms; the radical can further comprise other functional groups such as carboxyl and hydroxyl.

v)



wherein

each **Y** is independently selected from the group consisting of C and N,

R_6 is selected from the group consisting of cyclopropyl, phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-fluoroethyl and ethyl;

R_7 is selected from the group consisting of H, amino, methyl,

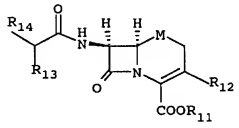
R_8 is selected from the group consisting of H and F;

R_9 is selected from the group consisting of H, methyl and a monovalent radical containing from 1 to 20 carbon atoms and from 1 to 4 nitrogen atoms;

R_{10} is selected from the group consisting of H, Cl and F;

R_6 e R_{10} can unite to form an optionally substituted six membered ring optionally containing up to two heteroatoms selected from the group consisting of oxygen and sulfur:

vi):



wherein

M is selected from the group consisting of sulfur, carbon or oxygen;

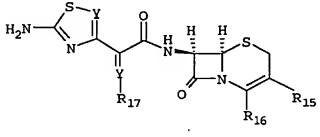
R_{11} is selected from the group consisting of H, pivaloyloxymethyl,

R_{12} is selected from the group consisting of chlorine and a monovalent radical containing from 1 to 5 carbon atoms, from 0 to 5 nitrogen atoms and from 0 to 1 sulfur atoms;

R_{13} is selected from the group consisting of amino, hydroxyl and monovalent radical containing from 1 to 10 carbon atoms, from 0 to 5 oxygen atoms and from 0 to 5 nitrogen atoms;preferably it is selected from the group consisting of amino, hydroxyl, carboxyl and

R_{14} is an unsaturated C_6 ring, optionally substituted;

vii)



wherein:

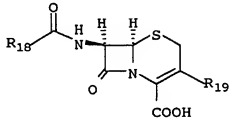
each **Y** is independently selected from the group consisting of carbon and nitrogen

$\mathbf{R_{15}}$ is selected from the group consisting of hydrogen and a monovalent radical containing from 1 to 12 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms;

$\mathbf{R_{16}}$ is a monovalent radical containing from 1 to 10 carbon atoms and from 2 to 8 oxygen atoms; preferably it is selected from the group consisting of carboxyl, $(CH_3)_3CCOOCH_2OCO$- and $(CH_3)_2CHOCOOCH(CH_3)OCO$-; when R_{15} is a quaternary ammonium cation, R_{16} is optionally a $-COO^-$;

$\mathbf{R_{17}}$ is selected from the group consisting of -OH and a monovalent radical containing from 1 to 12 carbon atoms and from 0 to 4 oxygen atoms, preferably it is selected from the group consisting of -OH, $-OCH_3$, $-CH_2CH_3$, $-OCH_2COOH$, $-CH_2COOH$, $OC(CH_2)_3$-COOH.

viii)

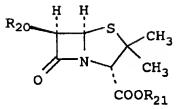


wherein:

$\mathbf{R_{18}}$ is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

$\mathbf{R_{19}}$ is selected from the group consisting of H and a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 6 nitrogen atoms and from 0 to 3 sulfur atoms;

ix)

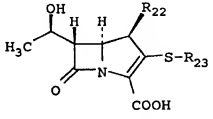


wherein:

R_{20} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms, from 0 to 3 fluorine atoms and from 0 to 3 chlorine atoms;

R_{21} is selected from the group consisting of H and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms;

x)

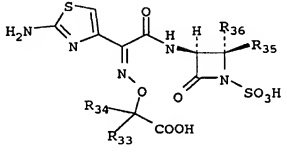


wherein:

R_{22} is selected from the group consisting of H and methyl;

R_{23} a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms and from 1 to 5 nitrogen atoms;

xi)

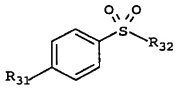


wherein:

R_{33} , R_{34} and R_{36} are independently selected from the group consisting of H and CH_3;

R_{35} is selected from the group consisting of H and $-CH_2OCONH_2$,

xii)

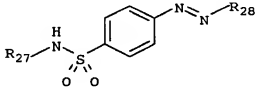


wherein:

R_{31} is selected from the group consisting of $-NH_2$, $-CH_2NH_2$ and $-NHCH_2Ph$

R_{32} is selected from the group consisting of $-NH_2$, $-NHR_{26}$ and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 5 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; wherein R_{26} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

xiii)

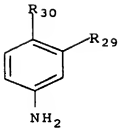


wherein:

R_{27} is selected from the group consisting of H and 4,6-dimethyl-2-pyrimidinyl;

R_{28} is a phenyl group substituted in at least 2 of the positions 2, 3, 4 and 6 by a group selected from hydroxyl, carboxyl and amino;

xiv)

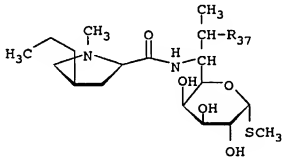


wherein:

R_{29} is selected from the group consisting of hydrogen and hydroxyl

R_{30} is selected from the group consisting of carboxyl, phenoxycarbonyl, 4-(amino)phenylsulfinyl, hydrazinocarbonyl;

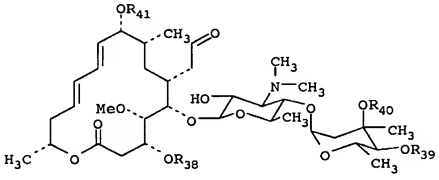
xv)



wherein:

R_{37} is selected from the group consisting of Cl and -OH;

xvi)

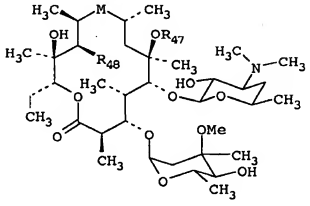


wherein:

R_{38} R_{39} R_{40} are independently selected from the group consisting of H and acyl; preferably they are selected from the group consisting of H, acetyl, propionyl, butyrryl, valeryl

R_{41} is independently selected from the group consisting of H and

xvii)



wherein:

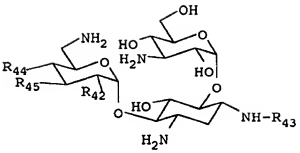
R_{47} is selected from the group consisting of H and $-CH_3$

M is selected from the group consisting of CO, N-methyl-aminomethylene and -CH(NHR$_{49}$)- wherein R_{49} is a substituted methylene bridge connecting N with R_{48}

R_{48} is hydroxyl or, when M is -CH(NHR$_{49}$)-, is -O-;

Preferably R_{49} is  ;

xvii)



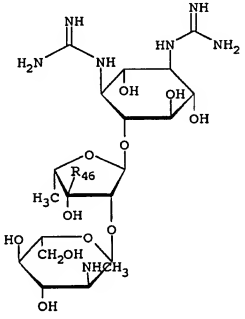
wherein:

R_{42} is selected from the group consisting of hydroxyl and amino;

R_{43} is selected from the group consisting of hydrogen, (R) and (S)-4-amino-2-hydroxybutyrryl

R_{44} and R_{45} are independently selected from the group consisting of hydrogen and hydroxyl.

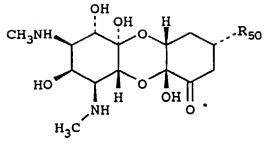
xviii)



wherein:

R_{46} is selected from the group consisting of $-CH_2OH$ and $-CHO$;

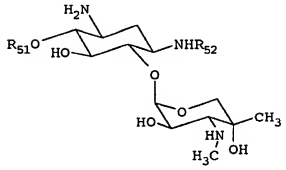
xix)



wherein:

R_{50} is a C_1-C_4 alkyl, preferably it is selected from the group consisting of methyl and n-butyl.

xx)

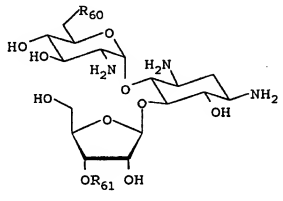


wherein:

R_{51} is independently selected from the group consisting of 3-amino-6-(aminomethyl)-3,4-dihydro-2H-pyran-2-yl and 2-amino-2,3,4,6-tetradeoxy-6-(methylamino)-α-D-eritro-hexopyranosyl,

R_{52} is selected from the group consisting of H and $-CH_2CH_3$.

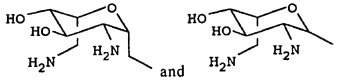
xxi)



wherein:

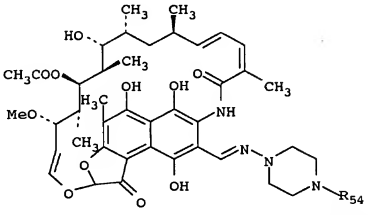
R_{60} is selected from the group consisting of –OH and $–NH_2$;

R_{61} is selected from the group consisting of H,



and

xxii)



wherein R_{54} is a C_1-C_4 linear or cyclic alkyl, preferably it is selected from the group consisting of methyl and cyclopropyl.

10. Composition according to claim 8 wherein the drug is selected from the group consisting of: Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, Paracetamol, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Ketorolac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen, Bermoprofen, CS-670, Zaltoprofen, Tenoxicam, Piroxicam, Meloxicam, Tenidap, Aceclofenac, Acemetacin, 5-amino-acetylsalicylic acid, Alclofenac, Alminoprofen, Amfenac, Bendazac, α-bisabolol, Bromosaligenin, Bucloxic acid, Butibufen, Cinmetacin, Clidanac, Clopirac, Diflunisal, Ditazol, Enfenamic acid, Etofenamate, Felbinac, Fenclozic acid, Fendosal, Fentiazac, Fepradinol, Flufenamic acid, Flunixin, Flunoxaprofen, Flurbiprofen, Glucametacin, Glycol salicilate, Ibuproxam, Isofezolac, Isoxepac, Isoxicam, Lornoxicam, Meclofenamic acid, Mefenamic acid, Metiazinic acid, Niflunic acid, Oxaceprol, Oxaprozin, Oxyphenbutazone, Parsalmide, Perisoxal, Olsalazine, Pirprofen, Protizinic acid, Salacetamide, Salicilamide O-acetic acid, Salsalate, Suxibuzone,

Tiaramide, Tinoridine, Tolfenamic acid, Tropesin, Xenbucin, Ximoprofen, Zomepirac, Tomoxiprol.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/15340

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 21193 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 May 1998 (1998-05-22) cited in the application claims	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 2002	11/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Berte, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 (1995-11-16) cited in the application claims	1-10
Y	WO 97 31654 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 4 September 1997 (1997-09-04) claims	1-10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-10 relate to an extremely large number of possible compounds. In fact, the claims contain so many variables or possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the examples and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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